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Original Article

Weekly robustness evaluation of intensity-modulated proton therapy for oesophageal cancer

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ABSTRACT

Background and purpose: Intensity-modulated proton therapy (IMPT) is expected to result in clinical benefits by lowering radiation dose to organs-at-risk (OARs). However, there are concerns about plan robustness due to motion. To address this uncertainty we evaluated the robustness of IMPT compared to the widely clinically used volumetric modulated arc therapy (VMAT) on weekly repeated computed tomographies (CT).

Materials and methods: 19 patients with oesophageal cancer were evaluated. IMPT and VMAT plans were created on a planning 4-Dimensional CT (p4DCT) and evaluated on weekly repeated 4DCTs (r4DCT). In case of inadequate target coverage or unacceptable high dose to normal tissue, re-planning was performed. Dose distributions of the r4DCTs were warped to p4DCT, resulting in an estimated actual given dose (EAGD).

Results: Compared to VMAT, IMPT resulted in significantly lowered dose to heart, lungs, spleen, liver and kidneys. For IMPT, target coverage was adequate (after max 1 replanning) in 17/19 cases. In two cases target coverage remained insufficient. However, in one of these patients the summed dose was insufficient (due to tumor shrinkage) while weekly coverage was adequate. For the other patient the target coverage was also insufficient by VMAT, due to large anatomical changes during treatment. For VMAT, adequate target coverage was achieved in 18/19 cases without re-planning. However, for reasons of high OAR dose re-planning was required in two cases.

Conclusion: IMPT reduces the dose to OARs significantly, while achieving adequate target coverage in the majority of patients. Re-planning was necessary for both IMPT and VMAT due to anatomical changes.

Radiotherapy plays a pivotal role in the curative treatment of oesophageal cancer patients [1]. However, thoracic radiotherapy is accompanied by serious risks of complications caused by dose to organs-at-risk (OARs), particularly to the heart and lungs [2–5]. Despite the development of new photon-based technologies, such as intensity modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT), radiation dose to normal tissues is still substantial [6].

Proton therapy (PT) reduces the normal tissue dose compared to the current standard photon therapy, due to its steep dose gradient. Several proton planning studies have shown the possibility to decrease the dose to OARs, such as heart, lungs and bone marrow, as compared to photon techniques [7–13]. The use of passive scattering proton therapy (PSPT) resulted in a decrease in postoperative complications compared to 3D conformal radiotherapy (3D-CRT) and IMRT [14]. Moreover, in the setting of definitive chemoradiotherapy, a survival benefit was seen after two and five years [15]. Intensity modulated proton therapy (IMPT), using pencil beam scanning (PBS) delivery, decreases the dose to OARs even further, compared to PSPT [16].

However, clinical implementation of IMPT for thoracic indications faces several challenges [17,18]. This modality is more sensitive to density changes in the beam path, potentially increasing the risks of over and under dosing. Density changes can occur during treatment due to cardiac action, breathing motion, changes in gastric filling or other general anatomical changes. Furthermore, the movement of the target and OARs caused by breathing, could interfere with the time structure of dose delivery, potentially resulting in dose inhomogeneities (interplay effects). This is especially true for distal oesophageal cancers that move markedly in craniocaudal direction due to breathing motion [19].

The OAR dose sparing capabilities of IMPT in the treatment of oesophageal cancer are promising, while clinical implementation

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is impeded by uncertainties caused by anatomical changes and breathing motion. Therefore, our aim was to evaluate the robustness of IMPT for distal oesophageal cancer, in terms of target coverage and normal tissue dose, during the full length of the treatment, compared to our current standard photon radiotherapy technique (VMAT).

Materials and methods

Patients

Twenty consecutive patients with histologically proven oesophageal cancer were included for this in silico planning study. These patients, over 18 years of age and with an WHO performance score of 0–2, were scheduled for neo-adjuvant (nCRT) or definitive (chemo)radiotherapy (d(C)RT). All patients were staged according to the TNM 7 [20]. This study was approved by the Medical Ethical Committee and all patients provided written informed consent (clinicaltrial.gov NCT03024138).

Imaging and image registration

Prior to their treatment, all patients underwent a planning 4DCT scan (p4DCT) with oral contrast, followed by weekly repeat 4DCT scans (r4DCT) without contrast agents, during treatment. The scans were performed on a 64-slice CT scanner (Somatom AS Open 64-RT Pro, Siemens Medical Systems, Erlangen, Germany), with 2-mm slice thickness and an in-plane resolution of 1.0 mm. Patients were positioned using an arm rest. An Anzai belt (Anzai Medical, Tokyo, Japan) was used to monitor the respiratory motion. The CT images were reconstructed into 10 respiratory phase bins and an average CT (av_p4DCT, av_r4DCT). The av_p4DCT was registered to each av_r4DCT by rigid registration focused on bony anatomy (similar to CBCT-based repositioning) and a deformable image registration (DIR) was performed, using the ANACONDA algorithm [21], in the RayStation treatment planning system (TPS) (v4.99, RaySearch Laboratories, Stockholm, Sweden).

Delineation

The gross tumor volume of the primary tumor (GTVp) and pathological lymph nodes (GTVn), were delineated by a radiation oncologist on the av_p4DCT, using all diagnostic information (CT, positron emission tomography (PET) CT, endoscopy, endoscopic ultrasound). The GTVp was expanded to a clinical target volume (CTVp), to encompass the mediastinal fatty tissue surrounding the tumor volume for over 3 cm craniocaudally, following the oesophageal or gastric mucosa. For creation of the CTVn, the GTVn was expanded 7 mm, excluding anatomical borders [22]. Next, an internal target volume (ITV) was created to encompass the CTV in all respiratory phases of the 4DCT. Finally, a planning target volume (PTV) was generated using a uniform expansion of the ITV of 8 mm to account for setup uncertainties. The following OARs were delineated: lungs, heart, spinal cord, liver, spleen and kidneys. Thereafter, all the target volumes were warped from the av_p4DCT to the av_r4DCTs, using DIR. The warped GTVs, CTVs and ITVs were evaluated and manually adjusted if necessary. Original copies of all warped structures were preserved for subsequent analysis. OARs were delineated on all av_r4DCTs for weekly dose evaluations. To evaluate the quality of the warped target volumes (ITV1) compared to the manually adjusted target volumes (ITV2), we calculated the conformity index (CI) as followed:

$$CI = \frac{ITV1}{ITV1 + ITV2} \times \frac{ITV2}{ITV1 + ITV2}$$

Treatment planning

For each patient, the clinically prescribed dose was used for treatment planning for both VMAT and IMPT plans. In our patient cohort three different dose prescriptions were used: 41.4 Gy (23 fractions of 1.8 Gy, nCRT), 50.4 Gy (28 fractions of 1.8 Gy, dCRT), or 51 Gy (17 fractions of 3 Gy, dRT). All treatment plans were made by two experienced radiation therapists (RTTs) on the av_p4DCTs, using the RayStation TPS. The oral contrast (HU >120) was overridden with 1.000 g/cm^3. The VMAT plans were created with Collapsed Cone, using two ipsilateral arcs. All VMAT plans were optimized, ensuring at least 95% of the prescribed dose coverage at 98% of the PTV. The following dose constraints (EQD2) were used for OARs: for the spinal cord, the maximum dose was D0.1 cm^3 $\leq$50 Gy, mean lung dose (MLD) $\leq$20 Gy, lung V5 $\leq$70%, lung V20 $\leq$30%, mean heart dose (MHD) $\leq$26 Gy, mean liver dose $\leq$20 Gy, mean spleen dose (MSD) $\leq$20 Gy, mean kidney dose $\leq$18 Gy. Hotspots of $\geq$107% of the prescribed dose were limited to 2 cm^3. For the IMPT plans, often three beam directions were chosen (one anterior, two posterior-oblique). During optimisation, auto-spot spacing was used to distribute the spots. The treatment machine had a spot size (in air at isocenter) of 3 mm (σ) at 230 MeV and a minimum energy of 70 MeV. Furthermore, a pencil beam dose algorithm was used for dose calculation. IMPT plans were robustly optimized on the ITV using the following settings: 8 mm for setup and 3% for range uncertainties [23,24]. All dose parameters are reported in Gy, assuming a relative biological effectiveness (RBE) of 1.1 for protons.

Robustness of all IMPT plans was evaluated by simulating 52 error scenarios (26 for VMAT), using 8 mm for setup uncertainties, and 3% for proton range uncertainties. Setup uncertainties were simulated by shifting the planning isocenter isotropically in 26 directions, with each 8 mm shift from the center to the surface of a sphere. The plans were accepted if the ITV D98 was >95% of the prescribed dose in the voxel-wise minimum dose distribution [25], and all normal tissue dose constraints were met in the nominal plan. For VMAT no robustness evaluation was performed on the final treatment plan.

Plan perturbations and evaluation

The VMAT and IMPT plans created on the av_p4DCT were recalculated on the weekly av_r4DCTs, simulating 26 error scenarios for photons or 52 for protons (2 mm for both setup uncertainties, and for IMPT 3% range uncertainties). The 2-mm setup uncertainty has been established from an internal assessment, accounting for imaging vs. treatment isocenter accuracy, as well as intrafractional setup errors. The voxel-wise minimum dose distribution was used to evaluate ITV D98 on each av_r4DCT, the voxel-wise maximum dose distribution was used to evaluate the spinal cord D0.1 cm^3, while the nominal plan dose was used to evaluate the other normal tissue constraints on each av_r4DCT. If the manually adjusted ITV D98 on an av_r4DCT was <94%, or the spinal cord D0.1 cm^3 was >51 Gy, normal tissue D0.1 cm^3 was >115% of prescribed dose, or the OAR thresholds were not met, re-planning was performed on that av_r4DCT. The adjusted plan was then recalculated on the remaining weekly av_r4DCTs, and evaluated as described above. For each patient, the total dose distribution delivered over the course of treatment was accumulated on the av_p4DCT. The computed dose per voxel for each av_r4DCT was warped to the av_p4DCT, accumulated and then evaluated. Dose was accumulated accounting 3–5 fractions per av_r4DCT, depending on the prescribed dose. This resulted in an estimated actual given dose (EAGD). After re-planning, the accumulation included the previously given fractions until plan adaption.

Statistics

Paired samples *T*-test was used to conclude whether differences in group means were statistically significant ($p \leq 0.05$).

Results

One of the 20 included patients withdraw the informed consent after one week of treatment and was excluded from further analysis. All remaining patients had mid- or distal oesophageal cancer. Patient characteristics are listed in Table 1.

Adequate target coverage was achieved in all patients for both VMAT and IMPT at baseline, with a mean coverage of 99% of the prescribed dose for the ITV D98. For one VMAT plan (no. 16), it was not possible to keep all dose constraints for OARs (lung V5 and V20, MHD) within the pre-defined boundaries due to the extensive volume of the PTV. For IMPT, all dose constraints were met and the MHD, MLD and MSD doses decreased with respect to the VMAT plan by on average 11.8 Gy (range: 6.2–16.0), 5.0 Gy (range: 2.0–11.2) and 5.2 Gy (range: 0.7–10.5), respectively. The heart V5 was decreased by 56% (range: 36–75) and the lung V5 by 33% (range: 8–60). The mean liver dose was decreased by 4.9 Gy, mean left kidney dose by 1.7 Gy and mean right kidney dose by 1.5 Gy. These differences were all statistically significant with a *p*-value of <0.01 (Table 2). Based on the NTCP model for postoperative pulmonary complications by Thomas et al. [26], the reduction in MLD would result in a risk reduction of postoperative pulmonary complications by 11% (range: 2–30%, p = <0.01).

For all 19 patients, the average estimated actual given dose (EAGD) ITV coverage without re-planning was 97% for VMAT and 93% for IMPT (range: 88–100% and 56–100%, respectively), resulting in adequate target coverage for 18 (95%) VMAT and 15 (79%) IMPT cases (Supplementary A). After one re-planning, ITVs for 18 (95%) VMAT and 17 (89%) IMPT cases were adequately covered (Fig. 1). Re-planning was required in five patients for VMAT according to an av_r4DCT, of which three might have been unnecessary in retrospect when considering the EAGD on the av_p4DCT (no. 4/8). In two cases, the normal tissue dose was too high (no. 5/16), however, for one case re-planning could not lower the normal tissue dose below threshold (no. 16). For this case, it remained impossible to achieve adequate dose coverage after re-planning. For 3 out of the 15 IMPT cases (no. 3, 5 and 15), re-planning was suggested based on inadequate target coverage in a specific week. However, in retrospect, when considering the final EAGD, this might have been unnecessary. In two patients, inadequate dose distribution was seen in the EAGD due to change in diaphragm position or pleural effusion, but adequate EAGD coverage was achieved after one re-planning (no. 5/8). In two cases, no adequate EAGD coverage could be achieved. In one case this was due to large changes in gastric filling while using a ventral beam (no. 2). In the other case an offset of diaphragm position resulted in reduced coverage (no. 16) (Fig. 2).

The EAGD MHD and MLD was significantly different from initial planned dose for both VMAT and IMPT. However, the EAGD Δdose

Table 1
Patient characteristics.

Characteristic		*n* (19)	(%)
Gender	Female	4	21.1
	Male	15	78.9
Age	Median (range)	68 (56–84)	
Tumor location	Mid-distal	1	5.3
	Distal	18	94.7
Stage	T2N0	2	10.5
	T2N1	1	5.3
	T3N0	4	21.1
	T3N1	8	42.1
	T3N2	3	15.8
	T4aN2	1	5.3
Treatment	41.4 Gy in 23 fx *	15	78.9
	50.4 Gy in 28 fx *	3	15.8
	51 Gy in 17 fx	1	5.3
GTV volume (cc)	mean (SD)	78 (±51)	
CTV volume (cc)	mean (SD)	280 (±134)	
ITV volume (cc)	mean (SD)	315 (±143)	
No. of r4DCTs	4	3	15.8
	5	14	73.7
	6	2	10.5

Abbreviations: fx: fractions, GTV: gross tumor volume, SD: standard deviation, ITV: internal target volume, r4DCT: repeated 4-dimensional computed tomography.
* Combined with weekly carboplatinum/paclitaxel.

Table 2
Dose to organs-at-risk (nominal baseline plan, without replanning).

Patient no.	Beam arcs/angles (°)		Spinal cord max (Gy)		Heart mean (Gy)		Heart V5 (%)		Lung mean (Gy)		Lung V5 (%)		Lung V20 (%)		Spleen mean (Gy)	
	VMAT	IMPT	VMAT	IMPT	VMAT	IMPT	VMAT	IMPT	VMAT	IMPT	VMAT	IMPT	VMAT	IMPT	VMAT	IMPT
1	0–180	0/160/200	38.60	31.81	19.80	6.17	96	24	9.17	3.65	60	17	11	6	6.53	1.68
2	0–180	0/160/200	35.84	31.37	13.76	5.70	58	22	3.94	1.64	20	7	4	3	16.50	6.17
3	0–180	0/145/215	25.35	28.77	19.78	9.64	98	40	9.77	4.48	65	23	13	8	9.09	6.43
4	0–180	0/145/215	28.00	24.40	20.91	8.25	100	37	9.27	4.50	53	24	13	8	18.34	16.68
5	0–180	0/145/215	41.74	23.42	25.93	13.13	99	47	11.39	6.03	69	31	18	12	4.25	0.00
6	0–180	0/160/200	39.75	35.96	22.99	7.02	100	27	10.57	1.87	69	9	10	1	0.71	0.00
7	0–180	0/150/210	47.22	48.33	23.20	11.89	95	55	11.53	4.95	69	23	15	10	11.84	7.92
8	0–180	0/145/215	41.73	28.61	21.91	6.56	79	26	4.83	2.85	24	16	6	4	0.71	0.00
9	0–180	0/150/210	30.02	29.77	17.14	10.72	92	42	8.45	4.03	53	20	13	7	13.30	9.10
10	0–180	0/140/210	38.29	26.75	17.83	6.52	76	28	5.51	2.63	31	12	6	6	19.03	8.53
11	0–180	0/150/210	43.41	33.89	14.22	5.06	70	18	6.00	2.73	36	15	5	5	5.75	1.85
12	0–180	0/150/210	34.18	31.59	20.19	8.56	99	31	8.28	4.33	53	20	10	8	12.16	7.03
13	0–180	0/145/215	35.83	26.53	17.10	4.98	97	22	7.79	4.78	49	25	9	8	6.21	1.04
14	335–180	0/150/210	40.40	30.47	16.37	7.11	80	29	5.18	2.56	26	13	7	2	7.34	4.12
15	0–180	0/150/210	29.52	28.76	21.16	7.19	100	31	9.79	4.20	67	24	10	5	10.91	1.95
16	0–180	0/150/220	39.08	32.56	28.30	15.59	100	55	19.38	8.19	100	42	35	15	19.75	11.65
17	0–180	0/150/220	38.27	33.65	25.02	10.34	100	43	11.51	4.78	67	27	17	3	17.31	6.84
18	0–180	0/150/220	36.18	19.10	15.84	6.58	84	29	7.23	3.33	44	20	4	3	8.94	3.17
19	0–180	0/150/220	35.78	34.87	24.74	11.71	100	47	12.20	6.18	66	33	23	9	19.44	15.31
Mean			36.80	30.56	20.33	8.56	91	34	9.04	4.09	54	21	12	6	10.95	5.76
Mean difference			6.24		11.76		56.32		4.95		32.63		5.58		5.19	
p-Value			<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001	

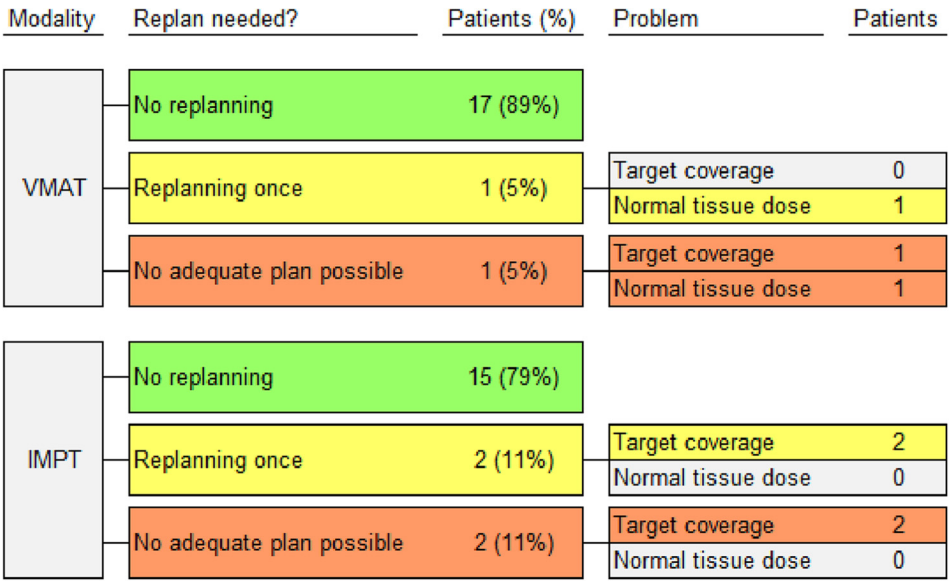

Fig. 1. Need for re-planning for VMAT and IMPT, based on estimated actual given dose.

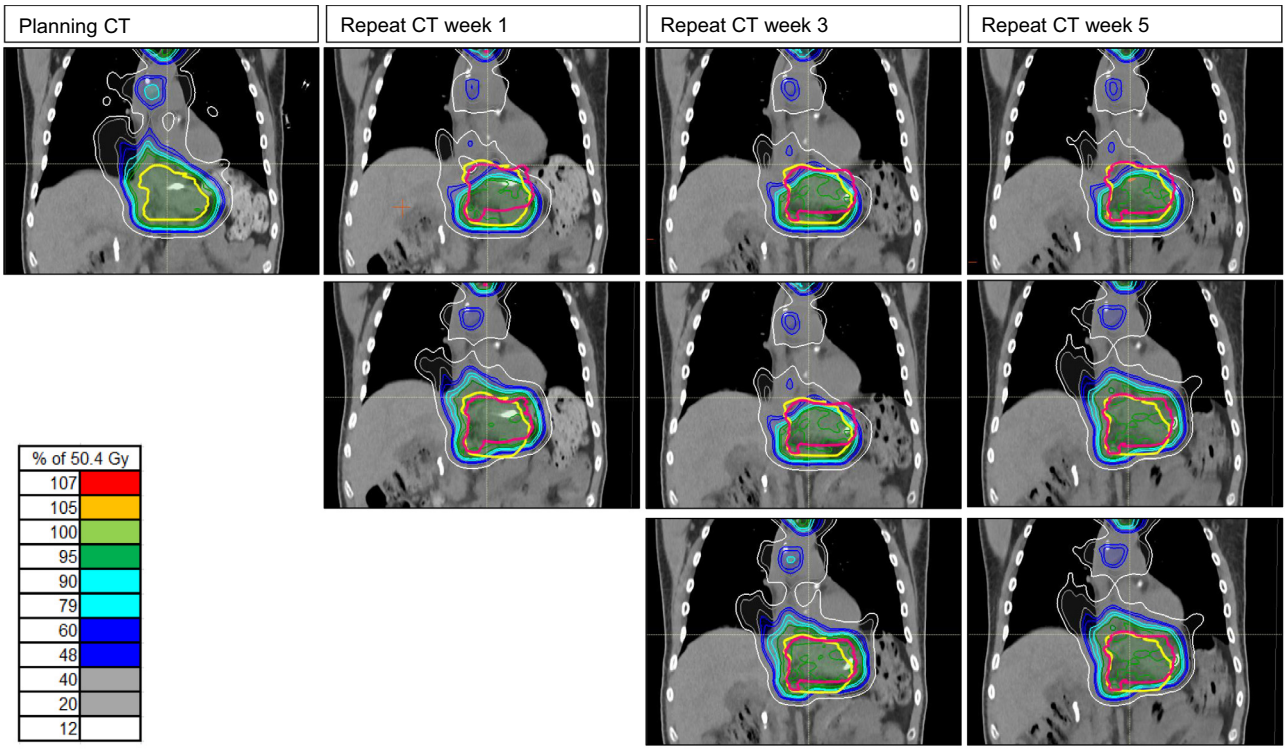

Fig. 2. Dose distributions of IMPT plans in coronal view for patient number 16. For the planning CT the nominal dose is shown with the original ITV (yellow). For the repeat CTs (rCT) the voxelwise minimum is shown, the warped ITV (yellow), and the manually adjusted ITV (pink). The first row shows the original plan, the second row shows the re-plan based on rCT1, the third row shows the re-plan based on rCT3.

MHD and MLD (between VMAT and IMPT) was not significantly different from the baseline Δdose (Fig. 3).

The mean baseline ITV was 316 cc (range 116–572) (Supplementary B). The CI between warped and adjusted structures was on average 0.86 (range 0.72–0.99). The need for re-planning was overestimated using the unadjusted warped ITVs on three rCTs (one VMAT, two IMPT), the coverage was sufficient after manual adjustment of the target. In contrast, there were three rCTs (one VMAT, two IMPT) where the need for re-planning was underestimated based on evaluation of the warped ITV, and re-planning was required based on evaluation of the manually adjusted ITV. However, this was considered only clinically relevant in one patient. For the other two patients, the underdosage remained restricted to air (dilated stomach), or the underdosage was detected in the last week only, and plan adaptation would not have been clinically relevant.

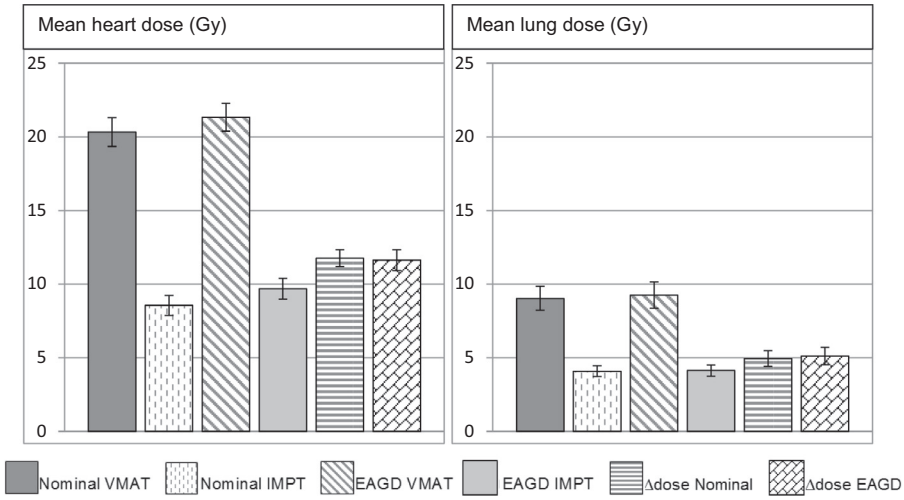

Fig. 3. Mean heart dose (left) and mean lung dose (right) for all patients for the nominal plan, the estimated actual given dose (EAGD) and the Δdose between VMAT and IMPT for the nominal plan and in the EAGD. The EAGD includes re-planning.

Discussion

In this unique dataset of weekly repeated 4DCTs, we have demonstrated that most IMPT plans (89%) for mid and distal oesophageal cancer patients maintained their robustness throughout the whole treatment course, however re-planning was needed more often compared to VMAT.

In our dataset, re-planning was indicated in two (11%) VMAT cases vs. four (22%) IMPT cases. Nyeng et al. previously showed that re-planning was required in 31% (9/29) of IMRT plans as a consequence of anatomical changes, based on one repeat CT [27]. In their population, the largest differences in dose coverage were caused by offsets in diaphragm position. More recently, Möller et al. evaluated multiple proton SFUD plans on one repeat CT and compared them to a standard IMRT plan [28]. In 6 of the 26 patients (23%), an offset in the diaphragm position was seen. The robustly optimized SFUD plans were more robust to these changes in diaphragm position than the IMRT plans. The authors explained this because they used posterior beams in SFUD, which avoids entrance through the diaphragm. These findings are in line with the results of Yu et al., who proposed a method to select beam angles that are least affected by diaphragmatic and respiratory motion, which reduces the risk of dose errors [16].

In the current analysis, reasons for re-planning were hotspots and inadequate target coverage, resulting from changes in diaphragm position, gastric filling or pleural effusion. The IMPT cases in which no adequate coverage was achieved, contained a ventrolateral beam, which is more vulnerable to changes in gastric filling. By choosing a beam setup without a ventrolateral beam, as performed in additional analysis (Supplementary C), this problem could be avoided.

Changes in gastric filling or pleural effusion can be detected by daily CBCT, and the impact can be mitigated by using adaptive radiotherapy. Offsets in diaphragm position can be more difficult to detect, requiring 4D(CB)CT reconstructions [29]. Anticipating planning strategies, such as the use of diaphragm or gastric filling overrides, might be useful to reduce potential dose errors [30]. Breathing motion mitigation techniques, such as breath-hold or mechanical ventilation, could reduce or regulate the breathing motion for patients with large offsets in diaphragm position [31,32]. For photon radiotherapy, robust optimisation and evaluation of the VMAT treatment plans might improve their robustness even further.

To our knowledge, this is the first study describing the estimated actual given dose (EAGD) evaluated using several weekly repeated 4DCTs for oesophageal cancer patients. Accumulated doses may provide insight in structural changes, whereas a single repeat CTs will also reflect incidental changes in anatomy. The final dose reduction to heart (average ΔMHD = 11.6 Gy) and lungs (average ΔMLD = 5.1 Gy) with the use of IMPT compared to VMAT was substantial, despite the changes in EAGD MHD and MLD. Moreover, the ΔMHD and ΔMLD did not change significantly over the course of treatment. These consistent dose reductions seem clinically relevant. Based on the model by Thomas et al. this MLD reduction would result in a risk reduction of postoperative pulmonary complications by 11% [26]. Retrospective series by the MD Anderson group also found a significant reduction in postoperative wound and pulmonary complications by use of PT [5]. More recently, the results of their phase II randomized controlled trial were published, which demonstrated that the dosimetric benefit of PT resulted in a clinically significant reduction of complications after neo-adjuvant chemoradiotherapy, especially in the postoperative total toxicity burden [33].

In the current study we evaluated plans that were optimized using a pencil beam dose calculation algorithm, which is widely clinical common practice. The absence of 4D-optimisation and Monte Carlo (MC) algorithms could be a limitation of this study. Recent studies suggested that the use of MC calculations results in a more realistic dose distribution [34]. However, it is unlikely that these MC calculated plans would perform worse than the current plans when evaluated on rCTs. According to Yu et al., 4D-optimized IMPT plans could increase robustness and mitigate the interplay effect of a single fraction [16], whereas Liu et al. performed an interplay effect evaluation on IMPT plans for distal oesophageal cancer, and found that the effects were small and clinically acceptable [35].

No robust evaluation of the VMAT plans was performed at baseline, as this was not clinical practice for photon treatment plans. Incorporation of robustness evaluation for VMAT into clinical practice might improve the target coverage on the rCT's for photon treatments as well [36]. This will have to be evaluated in following analysis.

Warping the delineations by DIR was adequate in most the cases. Moreover, the differences between warped and adjusted target volumes were in the same range as described delineation uncertainties between different observers [37,38]. However, a clin-

ical evaluation by a physician is essential to check for changes in anatomy that could compromise the warped structure, such as variations in diaphragm position or gastric filling.

In conclusion, IMPT resulted in comparable robustness of the treatment plans in terms of target coverage, compared to VMAT. A significant and consistent dose reduction to OARs could be achieved over the course of treatment by use of IMPT.

Conflict of interest notification

The department of Radiation Oncology has research agreements with IBA and RaySearch Laboratories. J.A. Langendijk received non-financial support and other from IBA and RaySearch Laboratories and a fee from IBA for giving a presentation at a symposium and giving consultancy. This has been paid to UMCG Research B.V. All other authors have no conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2020.07.015.

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